REMARKS

Claims 20-33 are pending. Claims 1-19 have been cancelled and new Claims 20-33 drafted for ease of examination. Support for new Claims 20-33 derives from the specification and claims as originally filed. Accordingly, the new claims do not present new matter and entry is proper.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-5 and 7-17 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner's main point appears to be that it is unclear how an *in silico* method results in proteins with altered immunogenicity.

Claims 1-5 and 7-17 have been cancelled, and thus, the rejection is moot. Applicants respectfully submit that this rejection does not apply to newly added Claims 20-33 as they are drawn to a method of screening for proteins with altered immunogenicity. Accordingly, Applicants respectfully request withdrawal of the rejection of Claims 1-5 and 7-17 under 35 U.S.C. § 112, second paragraph.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-5 and 7-17 are rejected for lack of written description. The Examiner's main point appears to be whether applicant was in possession of a method of modulating immunogenicity.

Claims 1-5 and 7-17 have been cancelled, and thus, the rejection is moot. Applicants respectfully submit that this rejection does not apply to newly added Claims 20-33 as they are drawn to a method of screening for proteins with altered immunogenicity comprising computational methods for generating a set of primary variant amino acid sequences that differ from the target protein, applying an immunogenicity filter to identify member of this set that have at least one variant immunogenic sequence, synthesizing and selecting a variant protein with altered immunogenicity. As acknowledged by the Examiner at page 5 of the Final Office Action, Applicants were in possession of computational methods for optimizing sequences and predicting binding to MHC molecules. In addition, Applicants submit

that they were in possession of methods for synthesizing and selecting a variant protein with altered immunogenicity at the time the application was filed. See, for example, the specification at page 44, line 7, through page 56, line 15.

Accordingly, Applicants respectfully request withdrawal of the rejection of Claims 1-5 and 7-17 under 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. § 103(a)

Claims 1-5 and 7-17 are rejected under 35 U.S.C. 103 (a) as obvious over Fleckenstein et al (Eur. J. Biochem., 240, 71-77, 1996) or Abrams (Current Opinions in Immunology, 12, 85-91, 2000; references C15 and C1) in view of Altuvia et al or Meister et al or Buus et al (references C2, C37, and C9) and in further view of Mayo et al (WO 98/47089 or US 6, 269,312).

Applicants assume that the following 12 rejections are being applied against Claims 1-5 and 7-17:

1) Fleckenstein in view of Altuvia;
2) Fleckenstein in view of Meister;
3) Fleckenstein in view of Buus;
4) Fleckenstein in view of Altuvia and further in view of Mayo;
5) Fleckenstein in view of Meister and further in view of Mayo;
6) Fleckenstein in view of Buus and further in view of Mayo;
7) Abrams in view of Altuvia;
8) Abrams in view of Meister;
9) Abrams in view of Buus;
10) Abrams in view of Altuvia and further in view of Mayo;
11) Abrams in view of Meister and further in view of Mayo; and
12) Abrams in view of Buus and further in view of Mayo.

While these rejections are argued together herein, the applicants retain the right to argue these rejections separately if required.

Fleckenstein teaches a method of identifying ligands that bind to the MHC class II molecule HLA-DRB1*0101 based on the activity pattern of an undecapeptide library. Thus, Fleckenstein discloses an experimental method for identifying ligands that bind to a specific MHC class II allele.

Altuvia discloses a structure based algorithm to predict potential binding peptides to four MHC alleles.

Meister teaches two computer-based algorithms, OptiMer and EpiMer, to predict peptides that stimulate T cell responses, termed T cell epitopes.

Buus describes recent advances in combinatorial peptide chemistry that have led to the improved description and prediction of peptide-MHC binding. These advances include experimental approaches for identifying binding motifs, statistical matrixes for classifying more or less preferred amino acids in simple natural or extended MHC binding peptide motifs, and artificial neural networks that can be trained to recognize peptides associated with binding to a given MHC molecule.

Abrams teaches recent advances in the cellular and molecular mechanisms of antigen recognition by CD8+ and CD4+ T lymphocytes that have led to experimental site-directed, rational modification of cognate antigenic determinants.

Both Mayo references cited by the Examiner teach computer methods for generating optimized protein sequences.

In contrast, the pending claims disclose a method of screening for altered immunogenicity of a target protein comprising an immunogenic sequence selected from the group consisting of sequences that bind to MHC class I molecules, MHC class II molecules, T cell epitopes or B cell epitopes. The steps disclosed in the method comprise: a) inputting the coordinates of said target protein into a computer; b) computationally generating a set of primary variant amino acid sequences using at least two scoring functions; c) applying a computational immunogenicity filter against said set to identify members of said set that have at least one variant immunogenic sequence; d) synthesizing a plurality of variant proteins each comprising at least one of said variant immunogenic sequences; and, e) selecting a variant protein with altered immunogenicity. Thus, this method requires distinct steps.

With respect to rejections 1-3 and 7-9 outlined above, the Examiner's position appears to be that one skilled in the art at the time the invention was made would be motivated to substitute the experimental methods disclosed by Fleckenstein or Abrams for identifying peptides that bind to MHC molecules with the computer algorithms taught by Altuvia, Meister, or Buus to arrive at a method for modulating immunogenicity.

With respect to rejections 4-6 and 10-12 outlined above the Examiner's position appears to be that one skilled in the art at the time the invention was made would be motivated to substitute the experimental methods disclosed by Fleckenstein or Abrams for identifying peptides that bind to MHC molecules with the computer algorithms taught by Altuvia, Meister, or Buus, further in view of the computerized methods of generating peptide libraries with substitutions at variable positions to arrive at a method for modulating immunogenicity.

Claims 1-5 and 7-17 have been cancelled, and thus, the rejection is moot. Applicants respectfully submit that rejections 1-12 outlined above do not apply to pending Claims 20-33.

As stated in M.P.E.P. §2142, a *prima facie* case of obviousness requires three basic criteria to be met. First, there must be some suggestion or motivation to practice the claimed invention. Second, the references taken alone or in combination, must teach or suggest all the claim limitations. Finally, there must be a reasonable expectation of success.

Applicants submit that there is no suggestion or motivation in Fleckenstein, Altuvia, Meister, or Buus to combine their respective teachings and to practice the claimed invention of screening for altered immunogenicity of a target protein because none of the cited references teach or suggest a screening method using a set of primary variant amino acid sequences generated from a target protein to identify a plurality of variant proteins each comprising at least one of variant immunogenic sequence.

Similarly, there is no suggestion or motivation in Abrams, Altuvia, Meister, or Buus to combine their respective teachings and to practice the claimed invention of screening for altered immunogenicity of a target protein.

Secondly, Fleckenstein, Altuvia, Meister, or Buus, or Abrams, Altuvia, Meister, or Buus do not teach all the claim limitations of pending claims 20-33. None of the prior art references teach a method for screening for altered immunogenicity of a target protein using a set of primary variant amino acid sequences generated from a target protein to identify a plurality of variant proteins each comprising at least one of variant immunogenic sequence as disclosed in the present invention.

Accordingly, Applicants submit that the above prior art references fail to meet at least two of the three criteria required to make a *prima facie* case of obviousness against pending claims 20-33.

Applicants submit that there is no suggestion or motivation in Fleckenstein, Altuvia, Meister, or Buus, further in view of Mayo to combine their respective teachings and to practice the claimed because none of the cited references disclose a method of screening for altered immunogenicity of target protein involving the steps of computationally generating a set of optimized protein sequences, and then applying a computational immunogenicity filter to members of this set to identify sequences that have at least one variant immunogenic sequence.

Secondly, Fleckenstein, Altuvia, Meister, or Buus, further in view of Mayo do not teach all the claim limitations of pending claims 20-33. As stated above, none of the cited references disclose a method of screening for altered immunogenicity of target protein involving the steps of computationally generating a set of optimized protein sequences, and then applying a computational immunogenicity filter to members of this set to identify sequences that have at least one variant immunogenic sequence.

Finally, Applicants submit that substituting Abrams for Fleckenstein does not result in the cited references teaching or disclosing a method of screening for altered immunogenicity of target protein involving the steps of computationally generating a set of optimized protein sequences, and then applying a computational immunogenicity filter to members of this set to identify sequences that have at least one variant immunogenic sequence.

Accordingly, Applicants submit that the above prior art references fail to meet at least two of the three criteria required to make a *prima facie* case of obviousness against pending claims 20-33. Withdrawal of the rejection of Claims 1-5 and 7-17 under 35 U.S.C. § 103 is respectfully requested.

Please direct further questions in connection with this Application to the undersigned at (415) 781-1989.

Respectfully submitted,
DORSEY & WHITNEY LLP

Dated: 2/26/04

By: Renee M. Kosslak

Four Embarcadero Center
Suite 3400
San Francisco, CA 94111-4187
Telephone: (415) 781-1989
Fax No. (415) 398-3249

Renee M. Kosslak, Reg. No. 47,717 for
Robin M. Silva, Reg. No. 38,304
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